
Nrf2, a regulator of the proteasome, controls self-renewal and pluripotency in human embryonic stem cells.

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Public Summary:

Nuclear factor, erythroid 2-like 2 (Nrf2) is a master transcription factor for cellular defense against endogenous and exogenous stresses by regulating expression of many antioxidant and detoxification genes. Here, we show that Nrf2 acts as a key pluripotency gene and a regulator of proteasome activity in human embryonic stem cells (hESCs). Nrf2 expression is highly enriched in hESCs and dramatically decreases upon differentiation. Nrf2 inhibition impairs both the self-renewal ability of hESCs and reestablishment of pluripotency during cellular reprogramming. Nrf2 activation can delay differentiation. During early hESC differentiation, Nrf2 closely co-localizes with OCT4 and NANOG. As an underlying mechanism, our data show that Nrf2 regulates proteasome activity in hESCs partially through proteasome maturation protein (POMP), a proteasome chaperone, which in turn controls the proliferation of self-renewing hESCs, three germ layer differentiation and cellular reprogramming. Even modest proteasome inhibition skews the balance of early differentiation toward mesendoderm at the expense of an ectodermal fate by decreasing the protein level of cyclin D1 and delaying the degradation of OCT4 and NANOG proteins. Taken together, our findings suggest a new potential link between environmental stress and stemness with Nrf2 and the proteasome.

Scientific Abstract:

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